Original Article

Asian Pacific Journal of Tropical Biomedicine

journal homepage: www.apjtb.org

doi: 10.4103/2221-1691.338921

Impact Factor: 1.55

Phloretin-induced suppression of oxidative and nitrosative stress attenuates doxorubicin-induced cardiotoxicity in rats

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ABSTRACT

Objective: To compare the cardioprotective efficacy of equimolar doses (50 mM/kg, *p.o.*) of phloretin and genistein against doxorubicin-induced cardiotoxicity in rats.

Methods: Cardiotoxicity was induced in rats by intraperitoneal injection of 6 mg/kg doxorubicin on alternative days till the cumulative dose reached 30 mg/kg. This study included four treatment groups of rats (n=6): the control group (0.5% carboxymethyl cellulose solution-treated), the doxorubicin-treated group (0.5% carboxymethyl cellulose solution along with doxorubicin), the genistein-treated group (50 mM/kg/day; *p.o.* along with doxorubicin) and phloretin-treated group (50 mM/kg/day; *p.o.* along with doxorubicin). On the 10th day of dosing, rats were anesthetized for recording ECG, mean arterial pressure, and left ventricular function. Oxidative stress, nitric oxide levels, and inflammatory cytokines were estimated in the cardiac tissue. Cardiac function parameters (creatine kinase MB, lactate dehydrogenase, aspartate aminotransferase, and alanine transaminase) were estimated in the serum samples.

Results: Phloretin treatment inhibited doxorubicin-induced oxidative stress and also reduced nitric oxide levels in cardiac tissues of rats. Phloretin administration attenuated doxorubicin-induced alterations in hemodynamic parameters (heart rate, mean arterial blood pressure, and left ventricular function) and suppressed the expression of pro-inflammatory cytokines. The cardiac injury markers like creatine kinase MB, lactate dehydrogenase, aspartate aminotransferase, and alanine transaminase were reduced by both genistein and phloretin. All these effects of phloretin were more prominent than genistein.

Conclusions: Phloretin offers cardioprotection that is comparable to genistein, a clinically validated cardioprotectant against doxorubicin-induced cardiotoxicity. Further studies are needed to confirm and establish the therapeutic utility of phloretin as a chemopreventive adjuvant to doxorubicin chemotherapy.

KEYWORDS: Cardiotoxicity; Chemoprevention; Doxorubicin; Genistein; Phloretin; Phytoestrogens; Cardiac injury; Hemodynamic changes

Significance

Considering the reported chemopreventive potential of phloretin, we compared the cardioprotective effects of equimolar doses of phloretin and genistein in the rat model of doxorubicin-induced cardiotoxicity. We noted better cardioprotection exhibited by phloretin as compared with genistein. This interesting activity profile projects phloretin as an important phytoestrogen with chemoprotectant action needing further preclinical and clinical evaluation against cancer chemotherapy-induced cardiotoxicity.

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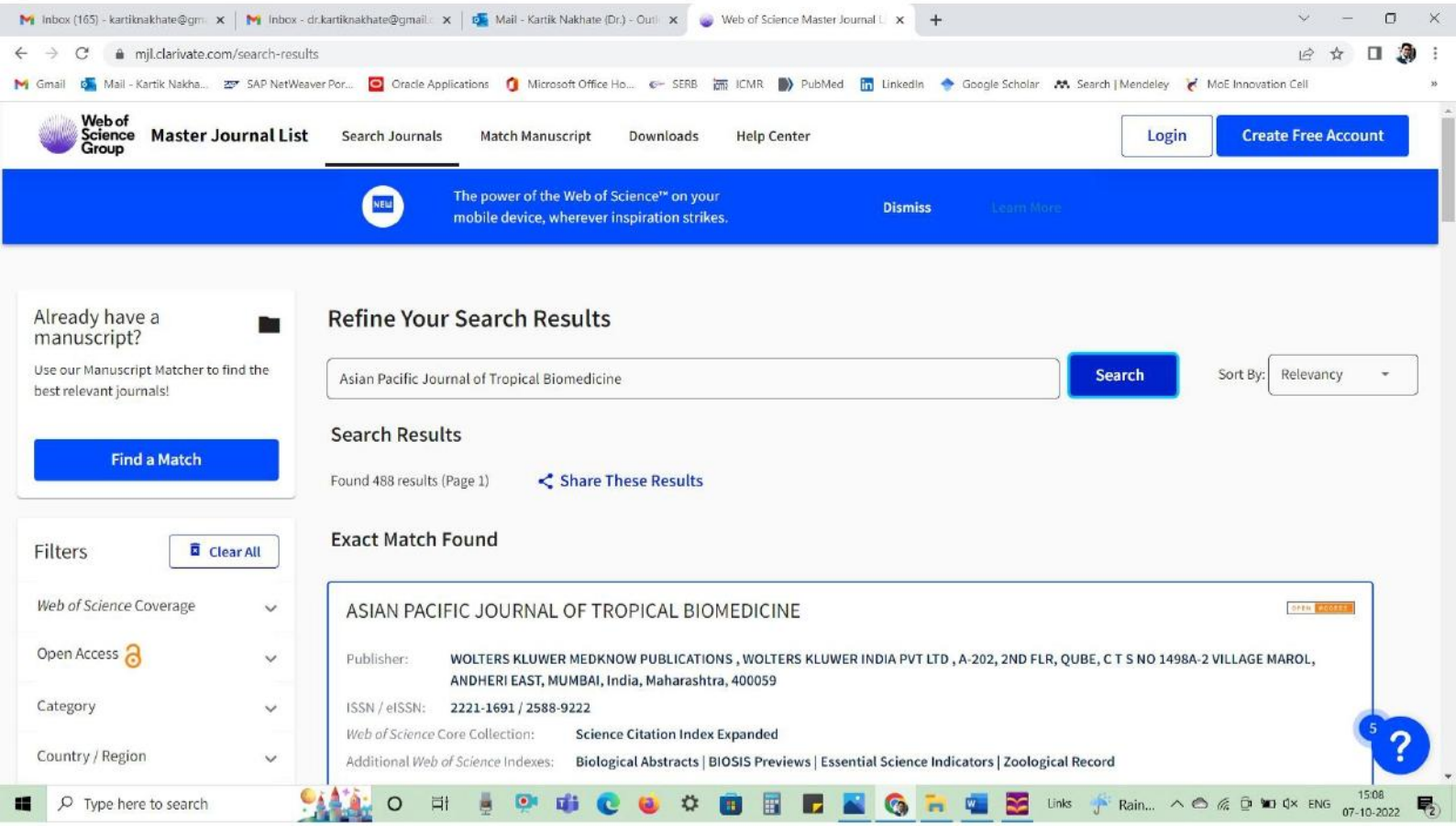
#Both authors have equal contribution.

How to cite this article: Wagh SS, Patil KR, Mahajan UB, Bagal PD, Wadkar AR, Bommanhalli B, et al. Phloretin-induced suppression of oxidative and nitrosative stress attenuates doxorubicin-induced cardiotoxicity in rats. Asian Pac J Trop Biomed 2022; 12(3): 124-131.

Article history: Received 19 May 2021; Revision 27 August 2021; Accepted 8 February 2022; Available online 10 March 2022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